II. REMARKS

Introductory Comments

Claims 1-13 were examined in the Office Action under reply and stand variously rejected under (1) nonstatutory double patenting (claims 1, 4, 8, 9, 10 and 12); (2) 35 U.S.C. §102 (claims 1-13); and (3) 35 U.S.C. §103(a) (claims 1-13). These grounds of rejection are believed to be overcome by this response and are otherwise traversed for reasons discussed in detail below.

Overview of the Above Amendments

Claims 8-10, 14 and 15 have been canceled. Claims 1-7 have been amended to recite that the vaccine is a "liquid" combination vaccine. Support for this amendment can be found at page 13, lines 24-19. Additionally, claims 1-7 now specify that the vaccine comprises an aluminium phosphate adjuvant, no more than 15% by weight of the Hib conjugate in the vaccine is adsorbed to aluminium phosphate, the vaccine does not contain an aluminium hydroxide adjuvant and the vaccine does not contain an aluminium potassium sulphate adjuvant. Support for these amendments can be found in original claim 8, as well as at page 6, lines 25-26. Moreover, claim 6 now specifies that the process comprises a step of attaching a label to a container. Support for this amendment can be found at page 3, line 10.

New claims 17-21 have been added. Claims 17 and 18 recite that at most 5% and 1%, respectively, of the Hib conjugate in the vaccine is adsorbed to aluminium phosphate and claim 19 specifies that the diphtheria toxoid and the tetanus toxoid are adsorbed onto aluminium phosphate. Support for these new claims can be found at page 6, lines 18-27. New claim 20 recites that the conjugate has a saccharide:protein ratio (w/w) of between 1:5 and 5:1. Support for new claim 20 can be found at page 4, lines 32-33. Finally, new claim 21 depends from withdrawn claim 16 and recites that administration of the vaccine results in an anti-PRP antibody concentration of $\geq$0.15 μg/ml. Support for this new claim can be found at page 5, lines 29-30.

The foregoing amendments are made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of

record. Applicant expressly reserves the right to file one or more continuing applications containing the unamended claims.

Request for Rejoinder

Applicant requests that withdrawn claim 16 and new claim 21 which depends therefrom, drawn to methods of using the compositions of elected Group I, be rejoined with the claims of Group I upon allowance of the product claims. This request is first presented prior to a final Office Action and prior to allowance of the application.

Rejections Over the Art

Claims 1, 4 and 8-13 were rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 7,348,006 and its corresponding U.S. Patent Publication No. 2005/0158334 to Contorni et al. The Office correctly notes the patent and publication have a common inventor with the present application and that these references can be overcome by eliminating the additional inventor on the '006 patent and the 334' publication by means of a Declaration pursuant to 37 CFR §1.132. Applicant is providing a Declaration of Inventorship that satisfies the requirements of MPEP §706.02(k)(C). Thus, the '006 patent and the '334 publication are not "an application for patent by another" and are therefore not properly citable art against the present application. Withdrawal of these bases for rejection is therefore respectfully requested.

Claims 1, 4, 5 and 8-13 were rejected under 35 U.S.C. §102(b) as anticipated by Nolan et al., *Vaccine* (2001) 19:2127-2137 ("Nolan"). The Office asserts Nolan describes a composition that includes DTP, a Hib conjugate (PRP-OMPC) and a hepatitis B vaccine, adjuvanted with aluminum phosphate. Paragraph 17 of the Office Action. However, applicant submits Nolan fails to anticipate the present claims.

To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). *Atlas Powder Co. v. E. I. du Pont De Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged as in the claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Connell v. Sears Roebuck & Co.*, 220 USPQ 193, 198 (Fed. Cir. 1983). Finally,

the law requires identity between the claimed invention and the prior art disclosure. *Kalman v. Kimberly-Clar Corp.* 218 USPQ 781, 789 (Fed. Cir. 1983, cert. denied, 465 U.S. 1026 (1984)).

All of the Hib-containing vaccines described in Nolan contain aluminium hydroxide adjuvants. See, page 21 of Nolan. Applicant's claims, on the other hand, expressly exclude the presence of an aluminium hydroxide adjuvant. Accordingly, Nolan does not anticipate the present claims and withdrawal of this basis for rejection is respectfully requested.

Claims 1, 4, 5, 8 and 11 were rejected under 35 U.S.C. §102(b) as anticipated by Nicol et al., *Pediatr. Infect. Dis. J.* (2002) 21:138-141 ("Nicol"). Applicant notes the Examiner calls this reference "Kaplan et al." Applicant assumes Nicol was intended as this citation matches Nicol and there is not a cited Kaplan reference on either applicant's Information Disclosure Statement or on the PTO-892 form that accompanied the Office Action. The Examiner reiterates verbatim the arguments presented in paragraph 17 of the Office Action regarding Nolan. However, as with Nolan, Nicol does not anticipate the present claims.

First, applicant cannot find anything in Nicol regarding a Hib conjugate that is PRP-OMPC as asserted by the Office. Rather, the conjugate used was a Hib polysaccharide-tetanus toxoid conjugate (PRP-T). Moreover, there was no hepatitis B vaccine included, as stated by the Examiner. Accordingly, applicant requests clarification regarding the Examiner's characterization of this reference. Moreover, the DPT vaccine used by Nicol was from Pasteur Merieux (see, page 139, column 1, 2nd full paragraph of Nicol). The Pasteur DPT vaccine includes diphtheria and tetanus toxoids, and killed *B. pertussis* organisms adsorbed onto aluminium hydroxide. See, the accompanying print-out describing the Pasteur Merieux DPT vaccine. As explained above, all of applicant's claims expressly exclude aluminium hydroxide. Finally, Nicol's vaccine contained 10 μg of the PRP and a dose of 0.5 ml was administered (see, page 139, column 1 of Nicol), making the concentration of the Hib in the vaccine 20 μg/ml. Applicant's claims, on the other hand, require that the concentration of Hib conjugate in the vaccine is <15 μg/ml. As explained at page 6, lines 7-10 of the specification, the concentration of a Hib conjugate is defined in terms of the mass of the saccharide. The

carrier is not included in this calculation in order to avoid confusion. Since Nicol's vaccine includes aluminium hydroxide and the amount of Hib in Nicol's vaccine is 20 μg/ml, Nicol also fails to anticipate the claims and withdrawal of this basis for rejection is also requested.

Claims 1, 4, 8 and 11-13 were also rejected under 35 U.S.C. §102(b) as anticipated by Eskola et al., *The Lancet* (1996) 348:1688-1692 (Eskola-1). The Office argues Eskola teaches methods for immunizing infants using a vaccine including a saccharide antigen of Hib conjugated to CRM197, tetanus and pertussis where the concentration of Hib is less than 15 μg/ml. However, as with the art described above, Eskola's vaccine composition includes aluminium hydroxide. Moreover, Eskola's vaccine also contained a dose of 20 μg/ml. See, page 1688, column 2 of Eskola. Thus, Eskola-1 does not anticipate the claims and withdrawal of this basis for rejection is respectfully requested.

Claims 1, 2, 4, 7 and 11-13 were rejected under 35 U.S.C. §102(b) as anticipated by Amir et al., *Vaccine* (1997) 2:149-154 ("Amir"). Additionally, claims 1, 2, 4 and 7-13 were rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent Publication No. 2003/0180316. Moreover, Claims 1-7, 11 and 12 were rejected under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Eskola et al., *The Lancet* (1999) 354:2063 (Eskola-2) and Black et al., *Pediatr. Infect. Dis. J.* (1993) 12:981-985 ("Black") in light of the disclosure in the US CDC documentation published on line. Applicant notes claim 8 was not subject to any of these rejections. The substance of claim 8 has been incorporated into all of the independent claims. Thus, these bases for rejection have also been overcome and withdrawal thereof is respectfully requested.

Claims 1-13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan "or and" Robinson, *Drugs of Today* (1993) 29:463-464 ("Robinson") "or" Eskola-2 and Black. Applicant is confused regarding this rejection. Is the rejection over Nolan or Robinson or Eskola-2 each taken with Black, or is the rejection over Nolan taken with Robinson and Eskola-2, further in view of Black? Additionally, the Examiner fails to point out the significance of Robinson. Applicant will address the rejection as if the

Examiner meant to recite the combination of Nolan with Robinson, Eskola-2 and Black. Applicant submits this combination does not render the present claims obvious.

Applicant's invention is based in part on the surprising finding that a liquid DTP-Hib vaccine containing a low dose of a Hib conjugate can survive prolonged storage when the vaccine is adjuvanted with aluminium phosphate rather than aluminium hydroxide. The general understanding in the art at the time of the priority date of the application was that Hib conjugates were unstable in aqueous media, and thus could not survive prolonged storage in aqueous form. For this reason, in combination vaccines that include Hib-conjugate antigens, it was common for the Hib component to be provided as a lyophilized powder that was reconstituted at the time of delivery with a liquid formulation of the other antigens. See, specification, page 1, lines 12-15. Moreover, the Hib concentration of the claimed vaccine is less than 15 μg/ml. Almost without exception, the standard vaccine dose of the prior art is 0.5 ml and the art cited by the Examiner gives the Hib concentration generally per dose, so that the amount of μg in the Hib dose described in the prior art is in fact twice as much when stated per ml. With this in mind, applicant submits the present claims are indeed nonobvious over the cited combination.

As explained in MPEP 2143, the rationale to support a conclusion of obviousness is that all the claimed elements were known in the cited art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. MPEP 2143 emphasizes that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966). Additionally, as set forth in MPEP 2142, impermissible hindsight must be avoided and the conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art. Based on these tenets, applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

First, none of the cited references provide for a vaccine with less than 15μg/ml

per dose. On the contrary, DTP-HbOC, the subject matter of Robinson and Black, has a dose of 20 μg/ml. See, the attached literature regarding Tetramune™, the tradename for DTP-HbOC. Moreover, Nolan, like Robinson and Black does not use less than 15 μg/ml per dose. Additionally, Nolan uses an aluminium hydroxide adjuvant. Finally, Eskola-2 is a review article concerning various DTP-Hib combinations. But Eskola does not describe the adjuvants in the vaccines tested. Nor does Eskola explain the doses administered.

One of skill in the art simply could not predict that a vaccine as claimed, with the particular components and doses claimed, would indeed be stable and efficacious. Eskola-2, cited by the Examiner, is indeed evidence of this fact. Eskola himself explains that physical interference between individual components of vaccines can account for immunogenic suppression. See, page 2063, 2nd column. Here, applicant has discovered that their liquid vaccine composition is stable and that a lower dose of Hib than previously used was effective. This could not have been predicted by one of skill in the art.

Thus, the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions" (*KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007)) Rather, as explained above, the evidence is to the contrary.

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

Nonstatutory Double Patenting

Claims 1, 4, 8, 9, 10 and 12 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12-17 of U.S. Application Serial No. 11/886,556. Applicant notes this rejection is provisional and hence premature as the purported conflicting claims have not in fact been patented and it is unclear at this time the ultimate claims that will be allowed. Accordingly, applicant requests the rejection be held in abeyance until allowable subject matter is indicated in this application. Applicant will then consider the propriety of filing a Terminal Disclaimer.

III. CONCLUSION

Applicant respectfully submits that the claims are now in condition for allowance and request early notification to that effect. The Examiner is encouraged to contact the undersigned if the Examiner notes any further matters which might be resolved by a telephone interview.

Respectfully submitted,

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